(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 July 2003 (10.07.2003)

PCT

(10) International Publication Number
WO 03/055538 A1

(51) International Patent Classification: A61M

(21) International Application Number: PCT/KR01/02254

(22) International Filing Date:
24 December 2001 (24.12.2001)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant and
(72) Inventor: JIN, Dong, Kyu [KR/KR]; Samsung Medical Center, Department of Pediatrics, 50 Ilwon-dong, Kangnam-ku, Seoul 135-230 (KR).

(74) Agent: KIM, Dong, Wan; 649-14, Yeoksam-dong, Kangnam-ku, Seoul 135-080 (KR).

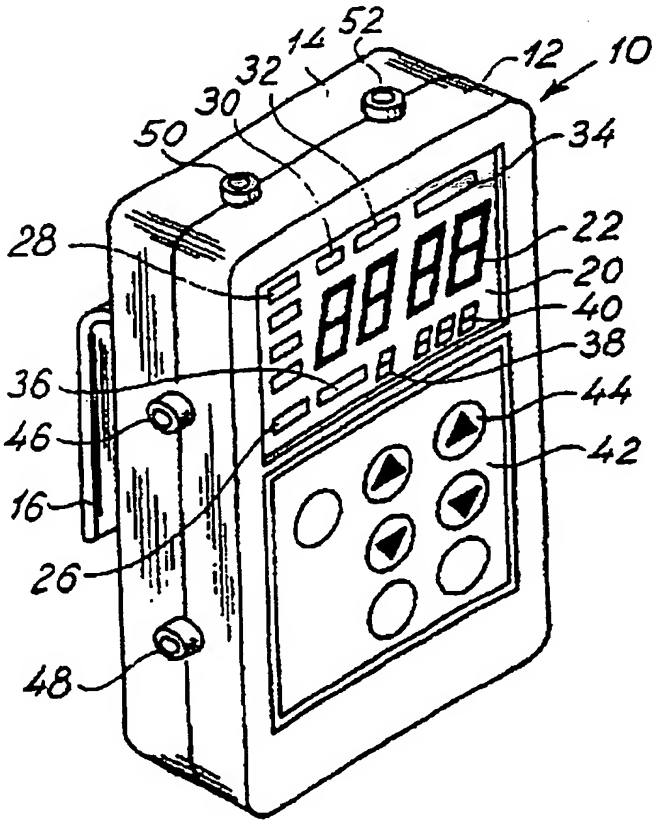
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INFUSION PUMP SYSTEM FOR INFUSION OF IDURONATE-2-SULFATASE RELIEVING HUNTER SYNDROME



(57) Abstract: The object of the present invention is to provide an infusion pump system for supplying iduronate-2-sulfatase to the Hunter syndrome patient, comprising: i) at least one infusion pump unit comprising a housing, a fluid inlet, and a fluid outlet; ii) an electronic control means received within said housing for controlling the operation of said controllable pumping system; iii) a power supply unit housed within said housing for supplying power; iv) a first capacitive detector circuit for detecting the presence of infusion liquid or alternatively air within the pumping system; and v) a stationary receptor system; wherein controllable pumping system is included within said housing and having an inlet and an outlet, and a receptor means for receiving and fixating said at least one infusion pump unit therein so as to maintain said at least one infusion pump unit in a stationary mode and exposing said fluid inlet and fluid outlet of said at least one infusion pump unit for allowing access.

WO 03/055538 A1

INFUSION PUMP SYSTEM FOR INFUSION OF IDURONATE-2-SULFATASE RELIEVING HUNTER SYNDROME

TECHNICAL FIELD

The present invention relates to a infusion pump system for relieving Hunter syndrome by supplying iduronate-2-sulfatase, which is deficient to the patient of Hunter syndrome.

BACKGROUND ART

The human body depends on a vast array of biochemical reactions to support critical functions, including the production of energy, growth and development, communication within the body, and protection from infection. Another critical function is the breakdown of large biomolecules, which is the underlying problem in Hunter syndrome.

Hunter syndrome is a rare lysosomal storage disorder affecting males that interferes with the body' s ability to break down mucopolysaccharides, which we will abbreviate as MPS. Hunter syndrome is also referred to as mucopolysaccharidosis Type II (MPS II) because it is one of several related lysosomal storage diseases.

The biochemistry of Hunter syndrome is related to a problem in a part of the connective tissue of the body known as the "extracellular

matrix." This matrix is made up of a variety of sugars and proteins and helps to form the architectural framework of the body. The matrix surrounds the cells of the body in an organized meshwork and functions as the glue that holds the cells of the body together. One of the constituents of the extracellular matrix is a complex molecule called a "proteoglycan." Like many components of the body, proteoglycans need to be broken down and replaced. When the body breaks down proteoglycans, one of the major breakdown products is a class of molecule known as a mucopolysaccharide (also referred to as glycosoaminoglycans, abbreviated as GAGs). There are several types of GAGs, each found in certain characteristic places in the body.

The symptoms of Hunter syndrome are not visible at birth, but usually start to become noticeable after the first-year of life. Often, the first symptoms may include inguinal hernias, ear infections, runny noses, and colds. Since these symptoms are quite common among all infants, they are not likely to lead a doctor to make a diagnosis of Hunter syndrome. As the build-up of GAGs continues throughout the cells of the body, signs of Hunter syndrome become more visible. Physical manifestations of some children with Hunter syndrome include a distinctive coarseness in their facial features, including a prominent forehead, a nose with a flattened bridge, as well as an enlarged tongue. Affected children may have unusually large heads as well as an enlarged abdomen. Many individuals continue to have frequent infections of the ears and respiratory tract.

The symptoms of Hunter syndrome range from relatively mild to severe. It is important to note that though the term "mild" is used by physicians in comparing patients with Hunter syndrome, the effects of even "mild" disease are quite serious. Two of the most significant areas

of variability concern the degree of mental retardation and expected lifespan. Many individuals who have Hunter syndrome are of normal intelligence and live into their 50s or 60s; there are reports of patients who have lived into their 80' s. The quality of life remains high in a large number of mildly affect patients; many adults are actively employed. In contrast, other patients develop severe mental impairment and have life expectancies of 15 years or less.

Hunter syndrome is quite rare, affecting approximately one in 100,000 people in the U.S. Since Hunter syndrome is an inherited disorder (X-linked recessive) affecting only males, it is passed down from one generation to the next in a specific way. Every cell in the human body has 46 chromosomes, with 23 derived from each parent. The I2S gene is located on the X-chromosome, which is the only chromosome that is different in males and females. Females have two X-chromosomes, one inherited from each parent, whereas males have one X-chromosome that they inherit from their mother and one Y-chromosome that they inherit from their father. This means that females have two copies of the I2S gene, but males only have one copy of the gene. Of note, the male Y-chromosome is never affected in Hunter syndrome.

If a male individual inherits an abnormal copy of the I2S gene from his mother he will develop Hunter syndrome. A male individual can inherit an abnormal copy of the I2S gene in one of two ways. His mother can be a carrier; i.e. she has one abnormal and one normal I2S gene, and she passes along the abnormal gene. Or a new mutation occurred in the I2S gene on the X-chromosome (inherited from the mother) when it was copied. In this second way, the mother is not a "carrier" and the risk for a recurrence is low. Females can carry one

abnormal copy of the I2S gene and are usually not affected. Hunter syndrome has been reported to occur in females, but is extremely rare.

Currently, there are no effective treatments for the underlying cause of Hunter syndrome or many of its symptoms. Current treatment is primarily supportive: hearing aids, physical therapy, and selected surgical procedures may be helpful in some patients.

For relieving Hunter syndrome, three kinds of treatment modalities can be considered. First, bone marrow transplantation was tried with some improvement of clinical symptoms. However, this therapy did not affect the neurological progression of the disease. Moreover, the transplantation associated mortality and morbidity is considerably high. Thus, most of the institute do not recommend bone marrow transplantation in Hunter syndrome. Second, gene therapy was tried in 2 patients living in Minnesota. But, the protocol was designed to give monthly intravenous injection of the retrovirus and was really cumbersome. Thus, 2 patients refused further treatment. Now, without the major progress in the technology of the gene therapy, there is no institute to consider the Hunter syndrome patient as a candidate for gene therapy.

Finally, enzyme replacement therapy is now being developed in several places in the world. The Hunter syndome is one of the lysosomal storage disorder and the receptor of the iduronate-2-sulfatase is related to mannose 6 phosphate ligands. These 2 characteristics of the Hunter syndrome make the disease a good candidate for enzyme replacement therapy like Gaucher disease. Gaucher disease is now being treated with enzyme. Enzyme replacement therapy is the standard regime worldwide. It is believed that soon or later, the enzyme replacement therapy of

idurodate-2-sulfate will become the standard therapy for the Hunter syndrome.

The production of iduronate-2-sulfatase (I2S) is possible by culturing the mammalian cells which produce high yield of recombinant iduronate-2-sulfatase. In our lab, we developed 2 cell lines for this purpose. One is from the COS cell and the other is from the CHO(chinese hamster ovary) cell line. We have transfected the iduronate-2-sulfatase c-DNA into the cells. For the COS cells, we transfected the plasmid containing iduronate-2-sulfatase with His tag (See Fig. 1). For the CHO cells, the plasmid contains iduronate-2-sulfatase c-DNA only(without His-tag). Both of the enzyme were effective when the recombinant enzyme was added to the fibroblasts from Hunter syndrome patients. GAG amount was lowered with both situations. So we want to administer the enzyme to the patients.

So far, the standard mode of infusion of recombinant enzyme is to use intravenous route. For example, the recombinant acid beta glucosidase is administered by intravenous route for 3 hours. However, if we want to use intravenous route for Hunter syndrome, that will be almost impossible because most of the hunter syndrome patients are mentally retarded and they will fight with medical staffs who try to administer it, otherwise we have to sedate them all the time, which is quite dangerous for the respiratory compromised Hunter syndrome patients.

In the present invention, we want to focus on the mode of infusion by pumping system. With, this pumping system, the infusion of iduronate-2-sulfatase is optimized. First, we can administer the enzyme at constant speed, not the bolus injection. Second, the system give us a survellence of the dosage, i,e, for the mentally retarded Hunter syndrome

patients, they are not aware of the total dose which has been already administered. The only way to moniter is to look at the panel of the pump. Third, the outer contour of the system is adjusted to fit it into the chest or abdomen or even back side by strapping the cloth which contain the pump itself. Fourth, the location of the needle is designed to optimized to the lower abdomen wall and backside. The skin of the Hunter syndrome patients is especially thick and do not allow small needle, thus we are using the thick needle with large pore inside. Moreover, the needle can be changed into intravenous one, like the depicted Figures.

For continuos and convenient supplying I2S to the patient, the infusion system of the present invention is designed as follows.

DISCLOSURE OF INVENTION

The object of the present invention is to provide an infusion pump system for supplying iduronate-2-sulfatase to the Hunter syndrome patient, comprising: i) at least one infusion pump unit comprising a housing, a fluid inlet, and a fluid outlet; ii) an electronic control means received within said housing for controlling the operation of said controllable pumping system; iii) a power supply unit housed within said housing for supplying power; iv) a first capacitive detector circuit for detecting the presence of infusion liquid or alternatively air within the pumping system; and v) a stationary receptor system; wherein controllable pumping system is included within said housing and having an inlet and an outlet, and a receptor means for receiving and fixating said at least one infusion pump unit therein so as to maintain said at

least one infusion pump unit in a stationary mode and exposing said fluid inlet and fluid outlet of said at least one infusion pump unit for allowing access.

In above infusion pump system, said electronic control means comprising a microprocessor control means; said electronic control means including display means for displaying the operational mode of the infusion pump unit and keyboard means for addressing said electronic control means; said electronic control means being programmable through an external program port; said electronic control means being pre-programmed.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 shows a construction of vector for expressing iduronate-2-sulfatase in the host cell.

FIG. 2 is a perspective and schematic view of presently preferred embodiment of a portable infusion pump unit for supplying iduronate-2-sulfatase to the Hunter syndrome patient according to the present invention,

FIG. 3 is an elevational and sectional view of embodiment of the portable infusion pump unit for supplying iduronate-2-sulfatase to the Hunter syndrome patient illustrated in FIG. 1,

FIG. 4 is a schematic view of the interior of embodiment of the portable infusion pump unit for supplying iduronate-2-sulfatase to the

Hunter syndrome patient illustrated in FIGS. 1 and 2, disclosing the flow path thereof,

FIG. 5 is a schematic view illustrating a possible application of embodiment of the portable infusion pump unit for supplying iduronate-2-sulfatase to the Hunter syndrome patient illustrated in FIGS. 1, 2 and 3,

BEST MODE FOR CARRYING OUT THE INVENTION

Preferred embodiment of a portable infusion pump unit for supplying iduronate-2-sulfatase to the Hunter syndrome patient is disclosed designated the reference numeral 10 in its entirety.

The apparatus 10 comprises a housing composed of two shell-like housing parts 12 and 14 constituting a front and rear housing part, respectively. The front an rear housing parts 12 and 14, respectively, are easily disassembled allowing the user to obtain access to the interior of the apparatus for substituting an interior fluid passage component to be described in greater detail below with reference to FIG. 3 constituting a disposable pre-sterilized component which is easily demounted after use and readily replaced prior to use. From the rear side of the housing part 14, a clip 16 allowing the apparatus 10 to be fixed to a strap or a belt extends. It is to be realised that terms such as upper, lower, front, rear, etc., unless otherwise stated, in the present context define positions or orientations determined by the intentional application of the apparatus 10 as the apparatus is positioned in an upright and substantially vertical position, e.g. received in the belt of a user by means of the clip 16 or

otherwise positioned exteriorly or non-implantatedly relative to the user.

In the front housing part 12, a display 20 is provided, comprising two sets of two digits designated the reference numerals 22 and 24, respectively, for displaying digits representing the time lapsed or the time remaining for infusion operation expressed in minutes and hours, respectively, or seconds and minutes, respectively, or alternatively for displaying digits representing the supply of infusion liquid as expressed in volume per time unit, e.g. ml per hour. The display 20 further includes a display area 26 for informing the user and/or a person operating the infusion pump apparatus 10 or nursing the user regarding the operational mode of the apparatus, such as standby or running information.

Furthermore, the display 20 includes a number of individual displays positioned above one another and above the standby/running display 26, one of which is designated the reference numeral 28. These individual displays 28 are adapted to display information such as the operational mode, e.g. the information that the apparatus is in a program mode, information regarding whatever information is presented on the two-digit displays 22, 24, such as the time remaining for infusion operation, the total time of the infusion operation, whether or not the apparatus is running or is to be started, or any other relevant information to be presented to the user or operator. The display 20 further includes three individual alarm displays 30, 32 and 34 for informing the user of the presence of air in the infusion pump circuitry, pressure fault or failure or low battery, respectively.

A further display 36 informs the user or operator of the program sequence presently used or programmed, which program sequence is

represented by a digit displaced by a 1-digit display 38. A 3-digit display 40 of the display 20 represents information to the user or operator regarding the infusion supply measured in ml per hour or similar relevant measure or ratio.

Below the display 20, a keyboard 42 is provided including a set of keys, one of which is designated the reference numeral 44 for allowing the user/operator to control the portable infusion pump unit 10 to perform a specific operation or to program the apparatus by shifting between specific program sequences by increasing a specific digit displayed in a 1-, 2- or 3-digit display, such as the displays 22, 24, 38 and 40, by increasing or reducing the digit in question and by shifting a cursor route relative to the various individual displays of the display 20 for allowing the user/operator to modify the operational mode or shift between various preset programs of the apparatus.

At the one side wall of the housing, composed by the housing parts 12 and 14 of the unit or apparatus 10, two terminals 46 and 48 are provided for allowing the apparatus 10 to be connected to an electronic charger for supplying electric power to an internal rechargeable battery pack or cell of the apparatus. The terminals 46 and 48 may alternatively or additionally serve as input/output terminals for establishing communication between the apparatus 10 and an external apparatus or equipment such as an external data logging apparatus or surveillance apparatus or further alternatively for communicating with an external processing unit such as a personal computer or data logging apparatus. Still further, the apparatus 10 may be provided with a conventional input/output terminal such as a conventional RS 232 terminal for establishing communication between the apparatus 10 and an external computer such as the above-mentioned personal computer for processing

data produced by the apparatus concerning the operational mode of the apparatus and also supplementary data produced by the apparatus or auxiliary equipment, e.g. data representing the temperature of the infusion liquid supplied by the apparatus 10 or data supplied by additional external measuring or surveillance equipment. In the top wall of the housing of the apparatus 10 two recesses are provided for receiving two tube connectors 50 and 52 constituting a fluid inlet and a fluid outlet, respectively, of the above-mentioned fluid passage component to be described in further detail below with reference to FIG. 4. As is evident from FIG. 3, a further fluid outlet 54 is provided in the bottom wall of the housing of the apparatus 10 opposite to the fluid outlet 52.

In FIG. 3, the interior structure of the portable infusion pump unit for supplying iduronate-2-sulfatase to the Hunter syndrome patient 10 is disclosed, illustrating the fluid inlet 50 and the fluid outlets 52 and 54. In FIG. 3, the reference numerals 56 and 58 designate two printed circuit boards including the electronic circuitry of the apparatus to be described, the rechargeable power pack or cell circuitry and the CPU-circuitry of the apparatus controlling the overall operation of the apparatus including the infusion operation. Alternatively, the electronic circuitry of the apparatus may be included in a single printed circuit board or, alternatively, three or more printed circuit boards. The internal rechargeable battery pack or cell is designated the reference numeral 60.

In FIG. 3, the internal flow system of the portable infusion pump apparatus 10 is disclosed, constituting a disposable and replaceable fluid passage component as mentioned above and including an inlet tube 62 connected to the fluid inlet 50. Two capacitive detectors 64 and 66 are mounted on the inlet tube 62 and communicate with the electronic circuitry of the apparatus housed on the printed circuit board 56 and 58

for detecting presence of air bobbles if any in the infusion liquid input to the fluid inlet 50. At its output end, the inlet tube 62 communicates with a first check valve 68 which constitutes an inlet to a pump housing component 70, in which an internal fluid passage is provided, as will be described in greater details below with reference to FIG. 4, which fluid passage terminates in an output or second check valve 72 from which two branched-off outlet tubes 74 and 76 communicate with the fluid outlets 54 and 52, respectively.

For transferring the infusion liquid or any other liquid input to the portable infusion pump unit 10 through the fluid inlet 50 to an application site through one of the fluid outlets 52 and 54, a piston type pump 78 is provided. The internal flow system of the portable infusion pump comprising the fluid inlet 50, the inlet rube 52, the capacitive detectors 64 and 66 belonging to the inlet tube 62, the first check valve 68, the pump housing component 70, the output check valve 72, the outlet tubes 74 and 76, and the outlets 52 and 54 constitute an integral disposable and replaceable fluid passage component.

In FIG. 4, the interior of the check valves and also the pump housing component 70 is disclosed in greater detail. The first check valve 58 basically comprises a central circular cylindrical housing component 80 from which a frustro-conical top part 81 extends upwardly communicating with the inlet tube 62 and arresting an inlet filter element 82 at the transition between the frustro-conical top part 81 and the cylindrical housing component 80. The cylindrical housing component 80 comprises a central annular oral component 84 which is sealed off in the initial or non-active position by a downwardly deflectable sealing membrane 86. Provided the pressure below the sealing membrane 86 is lower than the pressure above the membrane 86, the membrane 86 is

forced downwardly allowing liquid to pass through the central aperture of the central annular component 84 and further through apertures 87 provided offset relatively to the centre of the sealing membrane 86.

The first check valve 68 communicates with an inlet passage 88 of the pumping house component 70 terminating in an inner chamber defined within an upwardly protruding annular top housing component 90 in which a reciprocating plunger 94 of the piston pump 78 is movable in the direction to and from an abutting pin 96 which separates the inlet passage 88 from an outlet passage 98. The interspace between the reciprocating plunger of the piston pump 78 and the inner surface of the annular top housing component 90 is sealed by means of a highly flexible sealing gasket 92.

The outlet passage 98 communicates with the above described second check valve 72 which is basically of a configuration similar to and functioning as a check valve similar to the above described first check valve 58, however differing from the above described first check valve in that the second check valve 72 does not include any filter element similar to the filter element 82. The second check valve 72 includes a downwardly protruding annular housing part 100, which is cast integral with the pumping house component 70, fulfilling, however, the same purpose as the above described annular housing part 80 of the first check valve. From the annular housing part 100, a downwardly protruding frustro-conical housing part 101 similar to the above described frustro-conical housing part 81 extends communicating with the outlet tube 74 and similarly the outlet tube 76 described above with reference to FIG. 3.

Within the annular housing part 100, a sealing membrane 102

similar to the above described sealing member 86 is received, which includes apertures 103 similar to the apertures 87 described above. The sealing membrane 102 communicates with a conical bore 99 communicating with the outlet passage 98 for sealing off communication from the outlet passage 98, through the conical bore 99 to the outlet tube 74 provided the sealing membrane 102 rests against an abutting lower surface defining the lower boundary of the conical bore 99.

The pumping operation of the portable infusion pump unit 10 is established as follows. Initially, the first check valve 68 and the second check valve 72 are in their initial and sealing positions. It is also assumed that liquid is present within the inlet tube 62 within the inlet passage 88 and the outlet passage 98 and also within the outlet tube 74. The piston pump 78 is activated through the supply of an electric signal such as an alternating electric signal or a pulsed signal causing a solenoid within the piston pump to move the reciprocating plunger 94 upwardly or downwardly. The piston pump 78 is preferably, a piston pump in which the plunger 94 is biassed by means of a spring towards the exterior in relation to the housing of the piston pump and, consequently, downwardly in relation to the orientation of the piston pump 78 shown in FIG. 4.

The piston pump includes a bi-stable solenoid cooperating with the biassing spring of the piston pump for producing a controlled movement on the one hand generating adequate activation of the check valves 68 and 72 and at the same time preventing the generation of excessive pressure fluctuations within the pumping house component 70.

Assuming that the first movement of the reciprocating plunger 94 is in movement upwardly, a relative vacuum is created within the inlet

passage 88 and the outlet passage 98 by the increase of the volume defined below the sealing gasket 92. Through the creation of the relative vacuum within the inlet passage 88, the first check valve 68 is operated as the downwardly deflectable sealing membrane 86 is caused to move downwardly allowing liquid to flow into the inlet channel 88 through the central aperture of the central annular component 84 as described above. At the same time, the relative vacuum within the outlet passage 98 creates a relative vacuum above the sealing membrane 102 which is biassed so as to prevent free flow through the second check valve 72 urging or forcing the sealing membrane into sealing off and abutting engagement with a wall part circumferentially encircling and defining the conical bore 99, and consequently preventing liquid from being transferred from the outlet passage 98 to the outlet tube 74.

In summary, during the raising of the reciprocating plunger 94, the first check valve 68 is activated and caused to open whereas the second check valve 72 is blocked.

Above the second check valve 72, a bypass valve is provided, comprising a sealing membrane 104 which is acted upon by a central stem element 106 of a turnable knob 108 so as to force the sealing membrane 104 into sealing off and abutting engagement with a conical bore 105 provided above and in registration with the above described conical bore 99. Provided the conical bore 105 is sealed off by means of the sealing membrane 104, the bypass valve is not in operation. Provided the sealing membrane 104 is raised from its sealing off and abutting engagement with the conical bore 105 as the knob 108 is rotated for causing elevation of the actuator stem 106, communication from the outlet passage 98 is established through a bypass passage 110, bypassing the communication from the outlet passage 98 through the conical

passage 99 for allowing fluid to flow from the outlet passage 98 through the bypass passage 110 and further through the apertures 103 of the sealing membrane 102 which is consequently not functioning as the bypass valve is in operation.

The piston pump 78, which may constitute a replaceable component of the portable infusion pump unit or apparatus 10, may provide a specific stroke and, consequently, a specific flow volume per stroke. Therefore, the piston pump 78 is preferably provided with a switch or actuator cooperating with a switch of the electronic circuitry of the apparatus for informing the microprocessor of the electronic circuitry of the apparatus of the type of piston pump included within the apparatus at present. The technique of providing information to the microprocessor concerning the type of piston pump included within the apparatus at present may be established by means of numerous techniques well-known in the art per se such as by means of code switches, optic capacitive or inductive readers, or simply by means of a feedback circuit monitoring the work rate of the piston pump.

In FIG. 4, an inlet tube 112 is shown establishing communication from the inlet tube 62 through the fluid inlet 50 not shown in FIG. 4, however, shown in FIG. 3 from an infusion bag 114 which may constitute an infusion bag including an infusion liquid simply constituting physiological liquid or additionally or alternatively a drug suspended in any appropriate liquid, or alternatively blood plasma. The outlet from the outlet tube 74 of the portable infusion pump unit 10 shown in FIG. 5 is connected to an outlet tube 116 through the fluid outlet 54, not shown in FIG. 4, however, shown in FIG. 3, which external outlet tube 116 communicates with a cannular assembly 118 of a basically conventional structure.

The inlet tube 112 and the outlet cube 116 may constitute separate inlet and outlet tubes to be connected to the infusion pump unit 10 through the inlet and outlet 50 and 52 or, alternatively, 54, respectively. Alternatively, and preferably, the inlet tube 112 and the outlet tube 116 constitute integral components of the disposable and replaceable fluid passage component illustrated in FIG. 4, which fluid passage component is cooperating with and activated by means of the piston pump 78. Further alternatively, the infusion bag 114 may be configurated and housed within a container component which is configurated so as to allow the infusion bag 114 to be received and supported on top of the infusion pump unit or apparatus 10 as the above-mentioned receiver is simply connected to and supported by the housing of the portable infusion unit or apparatus 10.

The infusion of liquid from the infusion bag 104 is further illustrated in FIG. 5, in which the portable infusion pump 10 is received and fixed relative to an individual 120 by means of a belt or strap 122 on which the infusion bag 114 is further fixated. In FIG. 5, the external inlet tube 112, the external outlet tube 116 and the cannular assembly 118 are also illustrated.

WHAT IS CLAIMED IS :

1. An infusion pump system for supplying iduronate-2-sulfatase to the Hunter syndrome patient, comprising:
   - i) at least one infusion pump unit comprising a housing, a fluid inlet, and a fluid outlet;
   - ii) an electronic control means received within said housing for controlling the operation of said controllable pumping system;
   - iii) a power supply unit housed within said housing for supplying power;
   - iv) a first capacitive detector circuit for detecting the presence of infusion liquid or alternatively air within the pumping system; and
   - v) a stationary receptor system;

   wherein controllable pumping system is included within said housing and having an inlet and an outlet, and a receptor means for receiving and fixating said at least one infusion pump unit is therein so as to maintain said at least one infusion pump unit in a stationary mode and exposing said fluid inlet and fluid outlet of said at least one infusion pump unit for allowing access.

2. The infusion pump system for supplying iduronate-2-sulfatase to the Hunter syndrome patient according to claim 1, wherein said electronic control means comprises a microprocessor control means.

3. The infusion pump system for supplying iduronate-2-sulfatase to the Hunter syndrome patient according to claim 1, wherein said electronic control means include display means for displaying the operational mode of the infusion pump unit and keyboard means for addressing said electronic control means.

4. The infusion pump system for supplying iduronate-2-sulfatase to the Hunter syndrome patient according to claim 1, wherein said electronic control means is programmable through an external program port.

5. The infusion pump system for supplying iduronate-2-sulfatase to the Hunter syndrome patient according to claim 1, wherein said electronic control means is pre-programmed.

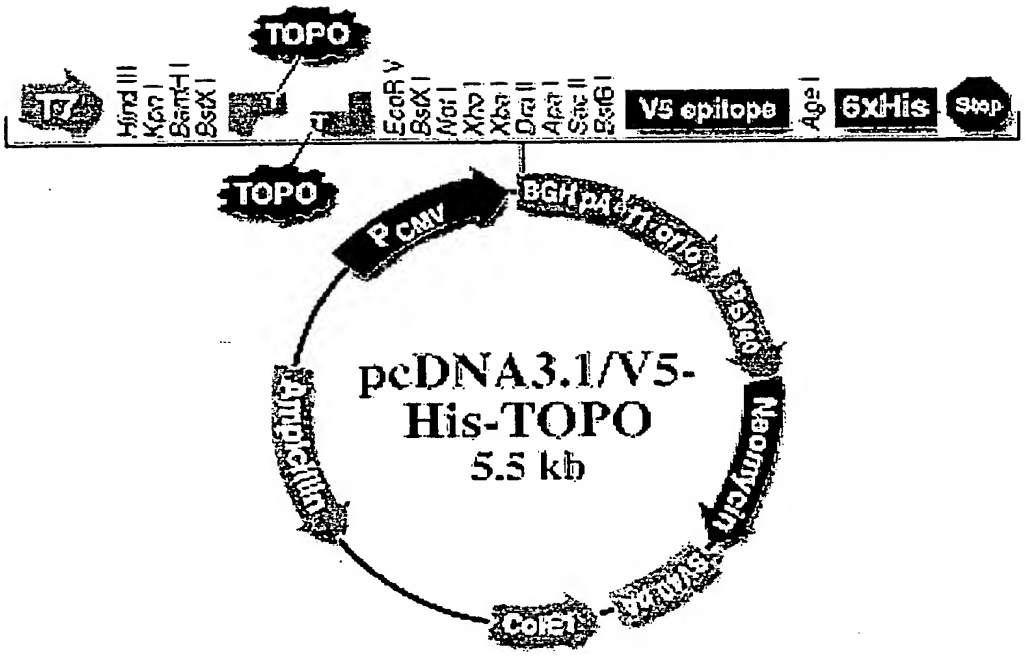

TOPO
Hind III
Kpn I
BamH I
BstX I
EcoR V
BstX I
Not I
Xho I
Xba I
Dra II
Apa I
Sac II
EcoR I
V5 epitope
Age I
6xHis
Stop
TOPO
P CMV
BGH pA
f1 ori
pUC ori
Neo/Kan
SV40 pA
ColE1
Amp
pcDNA3.1/V5-
His-TOPO
5.5 kb

FIG 1

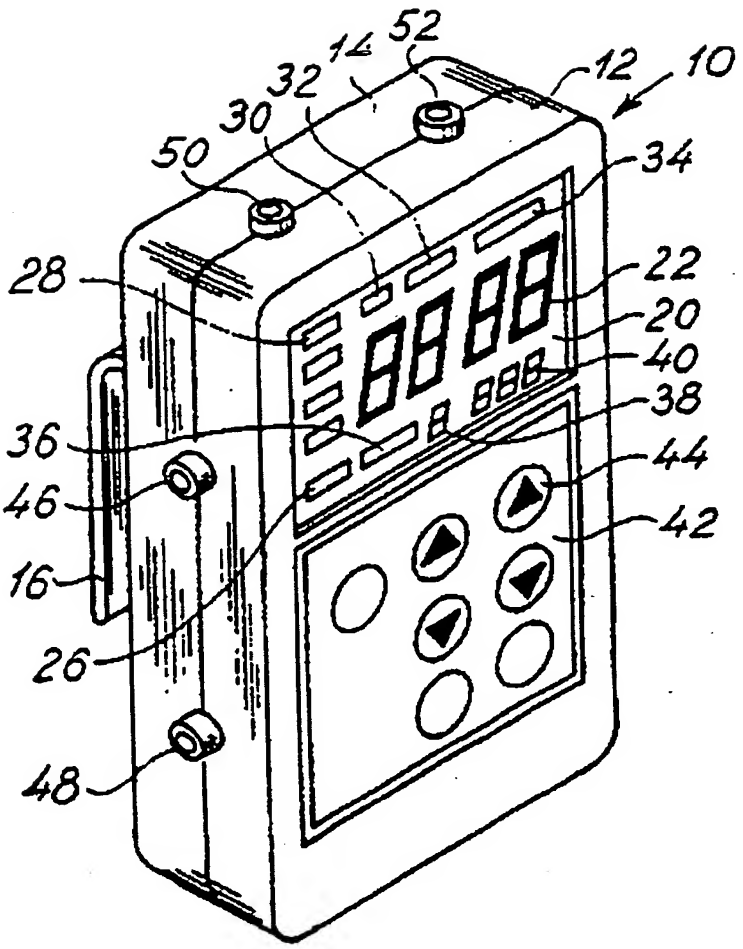


FIG 2

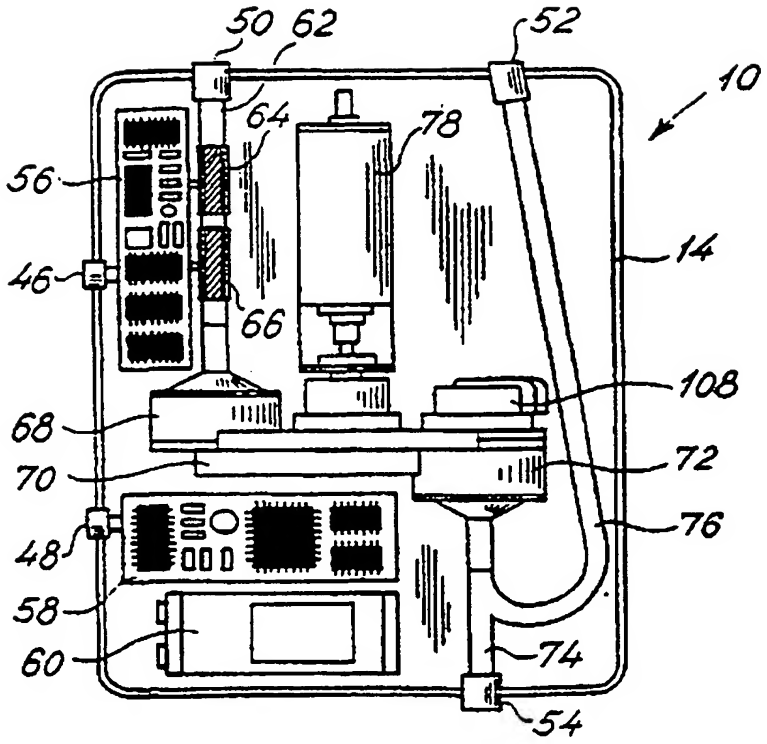


FIG 3

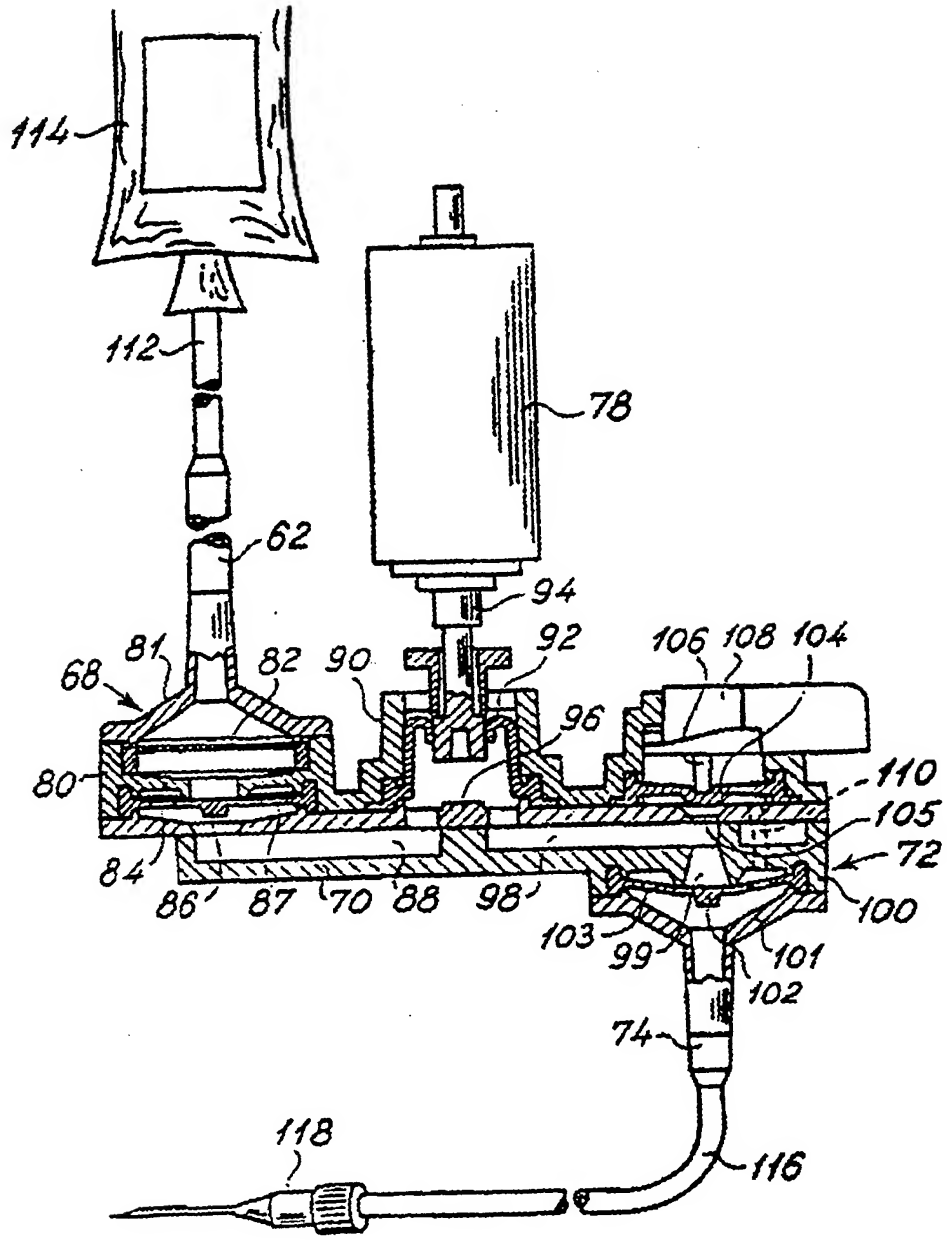

114
112
78
62
94
92
106
108
104
68
81
82
90
96
80
110
105
72
84
86
87
70
88
98
100
103
99
101
102
74
118
116

FIG 4

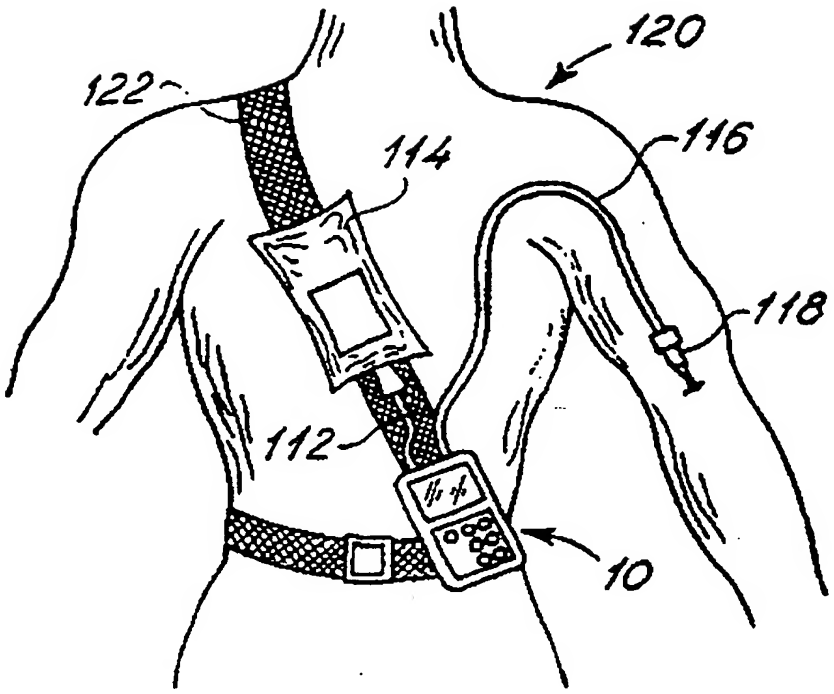


FIG 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 01/02254

CLASSIFICATION OF SUBJECT MATTER

IPC[7]: A61M 5/142

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: A61M 5/142

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6270478 B1 (MERNOE M.) 7 August 2001 (07.08.01) *the whole document; especially figures 1 - 4,8; claims 1 - 6.*	1-5
A	US 5932211 A (WILSON P. et al.) 3 August 1999 (03.08.99) *abstract; col. 1, lines 11-15, 32-43; col. 1, line 62 - col. 2, line 10; col. 8, lines 35-43; col. 8, line 64 - col. 9, line 15, col. 9, line 37 - col. 10, line 14; col. 10, line 66 - col. 11, line 13; claims 22, 28.*	1

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
„A" document defining the general state of the art which is not considered to be of particular relevance
„E" earlier application or patent but published on or after the international filing date
„L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
„O" document referring to an oral disclosure, use, exhibition or other means
„P" document published prior to the international filing date but later than the priority date claimed
„T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
„X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
„Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
„&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 March 2003 (04.03.2003)	12 March 2003 (12.03.2003)
Name and mailing adress of the ISA/AT Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer LUDWIG H. Telephone No. 1/53424/340

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR 01/02254

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US A 5932211	03-08-1999	US A 5728381	17-03-1998
		US A 5798239	25-08-1998
		US A 6153188	28-11-2000
US BA 6270478	07-08-2001	AU A1 96218/98	17-05-1999
		BR A 9812969	08-08-2000
		CA AA 2301534	06-05-1999
		EP A1 1024844	09-08-2000
		WO A1 9921596	06-05-1999